Soft Tissue Sarcoma Group at Helsinki University Hospital – First 25 Years, Lessons Learnt?

Antti Lehtonen
Lääketieteen kandidaatti
HUSLAB Meilahden patologian laboratorio

Helsinki 25.11.2020
Tutkielma
antti.i.lehtonen@helsinki.fi
Ohjaaja: Mika Sampo
HELSINGIN YLIOPISTO
Lääketieteellinen tiedekunta

HELSINGIN YLIOPISTO – HELSINGFORS UNIVERSITET

Tiedekunta/Osasto – Fakultet/Sektion – Faculty	Laitos – Institution – Department	
Lääketieteellinen tiedekunta	HUSLAB Meilahden patologian laboratorio	
Tekijä – Författare – Author		
Antti Lehtonen		
Työn nimi – Arbetets titel – Title		
Soft Tissue Sarcoma Group at Helsinki University Hospital – First 25 Years, Lessons Learnt?		
Oppiaine – Läroämne – Subject		
Lääketiede		
Työn laji – Arbetets art – Level	Aika – Datum – Month and year	Sivumäärä -Sidoantal - Number of pages
	25.11.2020	42 + 5

Tiivistelmä – Referat – Abstract

Pehmytkudossarkooma on harvinainen syöpätyyppi, johon luetaan 50 erilaista histologista alatyyppiä. Potilaiden mediaani-ikä on 60, ja syöpä on hieman yleisempi miehillä. Syöpä diagnosoidaan paksuneulabiopsialla. Ainoa kuratiivinen hoitomuoto on leikkaus, johon liitetään sädehoito, mikäli riittäviä leikkausmarginaaleja ei saavuteta. Riittävästä leikkausmarginaalista ei kuitenkaan ole konsensusta. Liitännäissolunsalpaajahoito parantaa hieman hoitotuloksia, mutta haittavaikutusten vuoksi siitä pidättäydytään suurimmalla osalla potilaista. Syövän ennustetekijöitä ovat potilaan ikä, tuumorin pahanlaatuisuusaste ja leikkausmarginaali. Syövälle altistavia tekijöitä ei aiempaa sädehoitoa lukuun ottamatta juuri tunneta.

Taudin harvinaisuuden, haasteellisen diagnostiikan, leikkaus- ja sädehoidon tarpeen sekä solunsalpaajahoidon monimutkaisen potilasvalinnan vuoksi on osoitettu, että hoidon keskittäminen parantaa hoitotuloksia. Sarkoomakeskukset noudattavat tarkemmin hoitolinjauksia; riittävään preoperatiiviseen kuvantamiseen, leikkausmarginaaleihin ja sädehoitoon päästään useammin, uusintaleikkauksiin päädytään harvemmin ja paikallisuusiutumien riski on pienempi. Tutkimusten mukaan kuitenkin vain noin kaksi kolmesta potilaasta lähetetään sarkoomakeskukseen ennen ensimmäistä operaatiota.

Tämän tutkimuksen tarkoituksena on toimia Helsingin yliopistollisen keskussairaalan (HYKS) Sarkoomaryhmän laaduntarkkailuna ryhmän ensimmäisten 25 vuoden ajalta. Tutkimuksessa keskitytään tarkastelemaan 1) hoitoprotokollan noudattamista, 2) pehmytkudossarkoomapotilaiden etäpesäkkeetöntä elossaoloaikaa ja kokonaiselossaoloaikaa ja 3) sädehoitoon liittyvän syövän hoitoa ja hoitotuloksia.

Aineisto koostuu HYKS:n Sarkoomaryhmään vuosina 1987-2012 lähetetyistä 1327:sta potilaasta. Aineiston potilaat on hoidettu sarkoomaryhmän vuonna 1987 laaditun hoitoprotokollan mukaan, joka pohjautuu Scandinavian Sarcoma Groupin hoitoprotokollaan.

1182 potilasta (79 %) lähetettiin sarkoomaryhmään primäärituumorin johdosta. Heistä vain 411 (35 %) lähetettiin ennen kajoavia toimenpiteitä; kajoamatta lähetettyjen potilaiden osuus kasvoi tarkastelujakson aikana 13 prosentista 47 prosenttiin. 1115 potilaasta, joiden hoitotavoite oli kuratiivinen, 680 (61 %) leikattiin kerran, osuuden kasvaessa ajan myötä. Niistä potilaista, joiden leikkausmarginaali oli positiivinen (kasvainta leikkausmarginaalissa) ja marginaalinen (pienin marginaali alle 2,5 cm), vain 64 ja 62 prosenttia sai adjuvanttia sädehoitoa. 5-vuotis- ja 10-vuotiselossaoloennusteet potilailla, joiden hoitotavoite oli

kuratiivinen, olivat 68 ja 55 prosenttia, eikä parannusta elossaoloennusteissa nähty tarkastelujakson aikana.

59 potilasta lähetettiin sarkoomaryhmään sädehoitoon liittyvän syövän johdosta, ja heistä 52 hoidettiin kuratiivisella tavoitteella. 77 prosentilla syöpä oli kehittynyt invasiivisen rintasyövän sädehoitoalueelle. Paikalliskontrollit 5-vuotis- ja 10-vuotisseurannassa olivat kuratiivisesti hoidetussa ryhmässä 73 ja 58 prosenttia.

Hoitoprotokollan noudattaminen HYKS:n Sarkoomaryhmässä on parantunut ajan yötä vuosina 1987-2012. Jotta ennen kajoavia toimenpiteitä sarkoomatyöryhmään lähetettyjen sarkoomaepäilyjen osuus kasvaisi, tietämystä pehmytkudossarkoomasta tulisi lisätä keskus- ja aluesairaalatasolla. Kaikki poikkeamat hoitoprotokollasta tulisi käydä läpi sarkoomatyöryhmässä ja kirjata potilasasiakirjamerkintöihin.

(342 sanaa)

Soft tissue sarcoma (STS) is a rare neoplasm consisting of approximately 50 different histologic subtypes treated similarly. The median patient age is 60 years, and there's a slight male predominance. There are no known predisposing factors apart from ionizing radiation. STS is diagnosed with core needle biopsy of a suspicious lump, most commonly a palpable, painless mass. Surgery with adequate margins is the only curative treatment of STS. Adjuvant radiation therapy (RT) improves local control rates (LC) and is offered for patients with positive surgical margins. However, there is no consensus on which surgical margin is wide enough. Adjuvant chemotherapy yields rather poor survival benefit with significant risk of toxicity and is therefore offered for minority of the patients. Prognostic factors for local recurrence include patient age, tumor grade and surgical margin.

Due to disease rarity, complex diagnostics, need for surgical treatment, adjuvant radiation therapy and critical evaluation of patient selection to receive chemotherapy, centralization of treatment is effective. Specialist centers adhere to treatment guidelines more strictly than non-tertiary centers. Adequate preoperative imaging methods are more often used, adequate surgical margins are more often achieved, patients undergo fewer operations, adequate adjuvant RT is more often offered and local control rates are better in specialist centers compared to non-tertiary centers. However, there is still a lack of adherence to referral policies with only 63 percent of STSs referred before surgical intervention.

The aim of this study was to quality control treatment received in Soft Tissue Sarcoma Group at Helsinki University Hospital (HUH) during its first 25 years, with special interest in

1) adherence to treatment protocol, 2) metastases-free survival (MFS) and overall survival (OS) of STS patients and 3) treatment and survival of radiation-associated STS.

We used a 1327-patient series from 1987-2012 consisting of patients referred to STS Group at HUH. Patients were treated according to treatment protocol based on 1987 Scandinavian Sarcoma Group recommendations.

1182 (79 %) patients had only primary tumor at presentation. Only 411 (35 %) patients referred for a primary tumor were referred untouched. However, the proportion increased by time from 13 to 47 percent. Of the 1115 patients treated with a curative intent, 680 (61 %) patients underwent only one procedure, proportion of which increased by time. Only 64 and 62 percent of patients with intralesional (tumor tissue in resection margin) and marginal margins (smallest margin under 2.5 cm) received adjuvant RT. Overall survival rates for patients treated with curative intent were 68 percent and 55 percent in 5-year and 10-year follow-up, respectively. No improvement in OS was recorded.

59 patients were referred for a radiation-associated sarcoma, and 52 of them were treated with a curative intent. Tumor appeared in the radiation field of an invasive breast cancer in 77 percent of the patients. Local control rates for patients treated with curative intent were 73 percent and 58 percent in 5-year and 10-year follow-up, respectively.

Adherence to treatment protocol in STS group at HUH has improved over time in 1987-2012. To increase the percentage of patients referred for primary tumor without preceding biopsy, increasing soft tissue sarcoma knowledge in district hospitals is vital. All exceptions from treatment protocol should be discussed and reported in patient files.

(530 words)

Avainsanat – Nyckelord – Keywords

Pathology; Sarcoma, Soft Tissue; Centralized Hospital Services; Survival

Säilytyspaikka – Förvaringställe – Where deposited

Muita tietoja – Övriga uppgifter – Additional information

Index

1 Introduction and Review of Literature

1.1 General

Soft tissue sarcoma (STS) is a rare neoplasm, constituting about 1 percent of all cancers with an annual incidence of approximately 1.4-3.33/10^5 [1-3]. The median age of patients at diagnosis is 60 years [1, 2, 4-7], and there is a slight male predominance in incidence: male-to-female ratio is about 1.1:1 [3-6].

The most common symptom of STS is a palpable mass, causing pain only in minority of the patients. Majority of tumors are deep-seated, most of which are larger than 5 cm in size [1]. The most common sites are thigh (the most common), trunk wall, upper arm and lower leg [1, 2, 4]. However, STS may occur in any extraskeletal site of the body. Currently, WHO Classification of Tumors of Soft Tissue and Bone includes over 50 histologic subtypes of STS [8]. In the largest patient series published, undifferentiated pleomorphic sarcoma (UPS), liposarcoma and leiomyosarcoma were the most common subtypes [7, 9, 10]. Treatment of local adult-type STS of the extremities and trunk wall is more or less the same despite of several histologic subtypes. Therefore, many patient series are restricted to these locations. Lungs are the most common site of first systemic relapse [11], and approximately 10 percent of patients have detectable metastases at diagnosis. Approximately 30 percent of patients develop pulmonary relapse during the course of the disease [11-13]. Most STS patients developing systemic disease die of the disease. However, a few patients developing systemic disease may be cured – or at least are long-term survivors – after even repeated complete removal of the disease. Lymph node metastases are rare and usually associate with clear cell sarcoma, UPS, and synovial sarcoma [14-16]. The median tumor size at diagnosis varies from 6 to 7 centimeters with a wide range depending on the location and depth [7, 17].

1.2 Etiology and Radiation-associated Sarcoma

Ionizing radiation is a known predisposing factor for STS, and a small subset of newly diagnosed STS patients carry a history of preceding therapeutic radiation therapy. Radiation-associated sarcoma (RAS) was first defined as sarcoma arising in bone in the radiation therapy field after a relatively long asymptomatic period before diagnosis of

sarcoma with histologic proof of sarcoma [18], and were later modified to include tissues adjacent to the path of the radiation beam and a latency period of at least 3-4 years [19]. Angiosarcoma (AS) has been the most common subtype in recent studies [20-25], whereas osteosarcoma and UPS were the most common types in older series [26].

1.3 Diagnostics

Diagnosis of STS is based on core needle biopsy (CNB) [27-32]. Fine needle aspiration is used in very few specialist centers with experienced experts in cytology, but otherwise its diagnostic accuracy has proven to be rather poor [32]. Free-hand CNB without imaging guidance (i.e. ultrasound) is an accurate biopsy method for palpable soft tissue tumors. Multiple tumor samples can be taken from a single needle puncture to obtain a representative specimen of a possibly heterogeneous tumor. Further, if an initial specimen is inadequate, CNB can be repeated. Possible advantages also include low costs and low complication rate. Strauss and colleagues state that image-guidance can, although, be used with necrotic or impalpable tumors [33].

Although incisional biopsy is the most precise method regarding diagnosis of malignancy, grade and histologic subtype, there is no significant difference between diagnostic accuracy of core needle biopsy and incisional biopsy. There seems to be a slight decrease in both sensitivity and specificity in grade determination and in sensitivity of malignancy diagnosis (96 percent) as well as definite sarcoma diagnosis (yes/no) (95 percent) in CNB compared to incisional biopsy (or the best standard diagnostic test) [31, 34]. Sensitivity of malignancy diagnosis and definite sarcoma diagnosis was 100 percent in Ray-Coquard and colleagues' 110-procedure series [34]. Ray-Coquard and colleaques concluded that CNB is accurate (or high degree of accuracy) and is not misleading (sensitivity 100 percent, specificity lower) [34]. In general, an adequate specimen is obtainable with core needle biopsy (88-93 percent compared to 100 percent with incisional biopsy) [30, 31]. In their recent paper, Strauss and colleagues observed accuracy of 97.6 percent (sensitivity 96.3 percent, specificity 99.4 percent) in differentiating malignant from benign soft tissue tumor at all sites with core needle biopsy [33]. Five of the eight false-negative diagnoses (CNB diagnosis was lipoma) were afterwards diagnosed as well-differentiated liposarcoma; a result that is in accordance with previous studies. However,

these neoplasms are occasionally difficult to differentiate from each other even when the final tumor resection sample is at disposal [33]. However, treatment approach is similar in these two entities, that is a simple enucleation. In addition, Strauss and colleagues showed that core needle biopsy is accurate in differentiating soft tissue tumor from soft tissue tumor like non-sarcoma malignancies, which is important because of totally different treatment pathways [33]. Mitsuyoshi and colleagues observed similar results: from adequate STS samples, malignancy could be determined in 94 percent (82 percent of all samples), and definite diagnosis was in 78 percent (68 percent of all samples) of the lesions [30]. Ray-Coquard and colleagues observed total concordance of core-needle biopsy and definite diagnosis of 88 percent of tumors; partial concordance was 7 percent while discordance was 5 percent [34]. Strauss and colleagues observed an accurate histologic subtype diagnosis in 88.0 percent of STSs and 89.5 percent in benign soft tissue tumors [33].

On the contrary, there is also rather recent evidence on the superiority of incisional biopsy compared to core-needle biopsy in everyday practice. In a 2000-2003 cohort from a national database in the Netherlands, a correct diagnosis of soft tissue malignancy (yes/no) was achieved with initial incisional biopsy, core needle biopsy and fine needle aspiration in 95 percent, 78 percent and 38 percent of the cases, respectively [32]. Although being the most accurate method, open biopsy has disadvantages such as operating room costs, increased morbidity and possible challenges it results for the definite operation, whereas core needle biopsy has lower morbidity (lower complication rates) and lower demand of resources. In addition, while core needle biopsy might not be as accurate as open biopsy, it can be performed several times in order to achieve an adequate specimen, and, if necessary, open biopsy can always follow [30, 31, 33, 34].

1.4 Treatment of Local Disease

1.4.1 Surgery

Surgery with clear margin is the only curative treatment of local STS. In a classic paper from 1981, surgical margins were divided into four categories based on studies on fascial boundaries and local recurrence (LR) rates in STS [35]. Modern classification is still widely based on this division. In the intralesional margin, tumor forms the periphery of

part or entire of the resection specimen. In the marginal margin, a pseudocapsule forms the periphery of the specimen. In the wide margin, a cuff of normal tissue forms the periphery of the specimen, and in the radical margin, all normal tissue of the compartment in question is resected en bloc together with the tumor. These four margins are applied to both excisions and amputations. Enneking's classification is widely used to describe surgical margins but there is controversy on how wide a normal tissue rim around the tumor is wide enough to yield sufficient local control (LC) without causing excessive functional impairment due to massive resections or amputations.

1.4.2 Adjuvant Radiation Therapy (RT)

In a randomized prospective study, patients with extremity tumors and a limb-sparing surgical option were randomized to receive or not to receive postoperative adjuvant external-beam radiation therapy after surgery with clear margin [36]. Significant decrease in the probability of local recurrence was seen with radiation therapy whereas radiation therapy had no effect on overall survival (OS). Another randomized study showed that preoperative radiation therapy (50 Gy in 25 fractions) and postoperative radiation therapy (66 Gy in 33 fractions) yielded same local control [37]. However, preoperative radiation therapy was associated with a greater risk of wound complications than postoperative radiation therapy [37].

1.4.3 Selection of Patients to Receive Adjuvant Radiation Therapy

Radiation therapy is not without adverse effects. There is no consensus on which patients should be offered radiation therapy to improve local control after surgery with clear margin, but surgical margin, grade, depth and size are the factors most frequently used for decision-making [38-42]. Surgery alone with wide margin of 1 or 2 cm is the most commonly used definition of adequate local treatment. In the report from Buffalo, New York on 171 patients with local STSs, adequate treatment was defined as either surgery with surgical margins of at least 2 cm alone (wide surgery) or surgery with smaller margins combined with postoperative radiation therapy [39]. Cut-off point value of 2 cm was arbitrarily chosen. Some groups recommend radiation therapy after surgery with margin of less than 1 cm or intralesional definite surgery [40, 41]. There are no strong data to support this cut-off value either. One open question is also who determines the

final margin – surgeon or pathologist. In a review of 111 patients comparing the smallest margin judged by the operating surgeon macroscopically and that by the pathologist microscopically, smallest margin measured less than 1 cm in approximately half of cases judged primarily by the surgeon to be wide, and in 10 percent of reviewed cases positive margins were identified among patients judged to have wide margin macroscopically [41]. Similar results have been published earlier [43-46]. This emphasizes the role of pathologist in STS treating team. Dickinson and colleagues concluded in their study on 279 patients with local STS that even with margins measuring approximately 1 mm, satisfactory local control can be achieved as long as the margins are not contaminated [47]. Smallest surgical margins of ≥ 1 cm and < 1 cm yielded local control rates of 100 percent and 87 percent in patients treated by function-saving surgery alone in a retrospective study from Boston [48].

Some groups have studied the area a little closer. Jebsen and colleagues evaluated the effect of radiation therapy on local control using Scandinavian Sarcoma Group registry [42]. In this 1,093-patient study, radiation therapy improved local control irrespective of tumor depth, grade, or surgical margin. Local control was most improved in deep-seated, high-grade tumors even if wide margin was achieved [42]. On the contrary, many subcutaneous soft tissue sarcomas can be safely treated by wide surgery alone as stated by the same group [49]. Similar result was present also in a prospective trial by Pisters and colleagues, aiming to define the local control rate of selected patients with T1 (size ≤ 5 cm) STS treated by surgery with clear margin alone [50]. They concluded that the local control of such patients with negative margins is acceptable even without radiation therapy. However, size should not be the only criterion for patient selection; instead, achieved margin should also be considered [50]. In Birmingham, radiation therapy is omitted only from patients with low-grade tumors excised with wide margin [51], whereas in Texas practically all patients are treated with adjuvant radiation therapy [52]. In Helsinki, the decision is made on the basis of surgical margin: patients having their tumor removed with a smaller than 25 mm margin and no natural barrier are systematically offered postoperative radiation therapy regardless of tumor grade [38, 53]. In some cancer centers, all patients with tumor larger than 5 cm are treated with adjuvant radiation therapy [54, 55]. Choong and colleagues [56] together with Yang and colleagues [36] recommend radiation therapy for both high grade and low grade tumors. The latter

contains however remark: when the expected toxicity of radiation therapy is high and risk of local recurrence is low based on surgical margin, tumor size, and location, conservative surgery without further treatment might be the treatment of choice [36]. In Scandinavia, the decision of adjuvant radiation therapy is based on surgical margin and depth of the tumor. Radiation therapy is strongly recommended also for patients with deep-seated, high-grade tumor although wide margin is reached [57]. Radiation therapy is delivered to all patients with high-grade lesions and with lesions of any grade in case of marginal surgical margins in Istituto Nazionale Tumori, Aviano, Italy [58]. On the contrary, in a retrospective paper based on the Surveillance, Epidemiology, and End Results (SEER) database, researchers concluded that surgery alone is safe for patients with T1 soft tissue sarcoma of the extremity [59].

In ESMO treatment guidelines, adjuvant radiation therapy is not recommended for patients with < 5 cm superficial tumors and < 5 cm deep low-grade tumors. However, radiation therapy is feasible for patients with < 5 cm deep high-grade tumors [60]. Nonetheless, there is evidence that surgery alone should be considered as adequate treatment for patients with stage 1 STS of the extremity (i.e. tumor < 5 cm) [59]. For neither low-grade nor high-grade tumors, surgery with adjuvant radiotherapy doesn't improve overall survival or sarcoma-specific survival compared to surgery alone [59].

1.4.4 Unplanned Surgery, Positive Margin, Use of Radiation Therapy

Unplanned excision in many cases seems to result in inadequate resection, so that microscopic or macroscopic tumor tissue is left in the tumor bed [51]. Patients referred to sarcoma centers after unplanned excisions have microscopic residual tumor left on resection margins in about 23.6-31 percent of the cases [61, 62]. The overall percentage is highly dependent on re-excision policies of separate treatment centers.

High-class surgery is still the first line treatment in STS and surgical margin is the only prognostic factor the surgeon and treatment team can affect. Positive surgical margin has a universally accepted adverse effect on local control [38, 41, 46, 63, 64]. Although radiation therapy serves as an effective adjunct modality to kill possible viable tumor

tissue or cells after surgery, it cannot wholly compensate for the adverse effect of positive margins on local control [46, 64, 65]. Furthermore, radiation doses required in this setting are generally higher. Contradictory results have also been published with Kim and colleagues concluding that re-resection may not be necessary for selected patients with microscopically positive margin when radiation therapy is administered [66]. On the other hand, the importance of re-resection and of clear margin, even if radiation therapy is routinely used, is emphasized [43, 52, 62]. Adjuvant radiation therapy is shown to improve local control among patients with positive definite margin [63, 67]. Local control of 76 percent at 5 years was reported among patients with positive margin and receiving adjuvant radiation therapy [67]. These patients were further analyzed by dividing them into 2 groups: patients with only microscopic tumor left in the operating bed (R1) versus patients with macroscopic tumor (R2) left. The former group had improved local control compared to the latter group, 81.3 percent vs. 67.1 percent ($p = 0.03$) [67]. Grade and size of the tumor had an independent impact on development of distant metastases and overall survival, but not on proceeding local control [67]. In a study of 110 patients with high-grade STSs of extremities having definite positive margin, the use of adjuvant radiation therapy improved local control from 56 percent to 74 percent [63]. However, improvement in metastases-free survival or overall survival could not be recorded [63].

Some groups have concentrated in their research also on independent predictors other than margin status of local control. Cahlon and colleagues observed 5-year local recurrence rate of 9 percent for the whole patient population [65]. Age more than 50 years and stage III disease were independent adverse predictors of local recurrence in patients with pathologically negative re-resection margins [65]. When evaluating the effect of risk factors (age ≥ 50, stage III disease), patients with no risk factors compared to those with 1 or 2 risk factors, the 5-year LR rates were 4 percent, 12 percent and 31 percent, indicating the possible need of radiation therapy in patients with higher-risk disease [65]. In another study, a high-grade tumor re-resected with a positive margin had a 67 percent local recurrence risk, whereas there was no notable difference in local recurrence rates with negative (23 percent) and wide (25 percent) re-resected specimens [51]. All other patients than those with high-grade, marginally re-resected tumor, had a risk of local recurrence of 19 percent [51]. Similar results were obtained by Rehders and colleagues: residual tumor after initial resection didn’t statistically affect local recurrence-free

survival after reresection with negative margins [61]. Fiore et al observed 10-year local recurrence rates of 17.5 and 19.2 percent for re-resected patients with residual disease on initial margins and those with no residual disease left, respectively, a result which is rather well in accordance with previous studies [62].

For patients with positive margins, radiation dose > 64 Gy improved local control in both extremity and other site tumors whereas the LC results of other site tumors receiving ≤ 64 Gy radiation dose were remarkably weak [67]. LC at five years was 85 percent compared to 66.1 percent [67]. For improved local control, the strongest predictors were extremity site and radiation dose > 64 Gy. One explanation of the favorable effect of the extremity site on local control is that in the extremities tumors resected with positive margins often have only microscopic tumor left compared to positive margins in other sites (for example retroperitoneum) where tumor residual may more frequently be macroscopic.

In case of positive (< 1 mm) or close (< 10 mm) margin, adjuvant RT may be considered as adequate treatment instead of reresection. In a 150-patient series comparing groups A (negative margins + RT) and B (positive/close margins + RT), there was no significant difference in 5-year local recurrence rates (A: 25.3 percent, B: 28.4 percent) or overall survival rates [66]. High tumor grade was the only significant predictor of local recurrence (5-year local recurrence-free rates: 62.3 percent and 90.8 percent, high grade vs low grade).

1.4.5 Adjuvant Chemotherapy

Randomized studies have repeatedly failed to show survival benefit from adjuvant chemotherapy for STS mainly because of low power, a modest effect and slow recruall of patients. In an 18-randomized controlled trial meta-analysis, adjuvant anthracycline-based combination chemotherapy significantly improved both relapse-free and overall survival in soft tissue sarcoma [68]. The overall risk ratio for mortality was a modest 0.77, which translated into an absolute risk reduction of 6 percent. The combination of anthracyclines and ifosfamide seemed to be the most efficacious combination, yielding a

relative risk reduction of 0.56 and an absolute risk reduction of 11 percent for mortality [68]. This moderate risk reduction must be weighed against toxicity. In an adjuvant randomized phase II study by the Canadian sarcoma group the combination of doxorubicin and ifosfamide was associated with a 29 percent incidence of grade 3-4 nausea and vomiting, and an 8 percent incidence of grade 3-4 hematological toxicity [69]. One patient (1.5 percent) died of neutropenic treatment associated infection. Addition of ifosfamide to regimen significantly improved the tumor response rate but didn't produce significant difference in one-year survival in a meta-analysis [70]. Adverse events, particularly grade 3-4 myelosuppression were observed more frequently in patients who received regimens that contained ifosfamide. Ifosfamide was recommended for advanced soft tissue sarcomas. Selection of patients (of patients with median age of 60 years and in many cases with several co-morbidies) to receive (neo)adjuvant chemotherapy is therefore critical.

1.5 Treatment of Locally Recurrent Disease

Isolated local recurrence, the frequency of which with modern multimodality therapy is approximately 10 percent, can in many cases be treated with curative intention. Previous local treatment makes the operation conditions more difficult because of changed anatomy and scarring. It is thus also more difficult to achieve adequate local control [71]. In isolated local recurrences treated surgically, the five-year local recurrence-free and overall survival rates were 72 percent and 77 percent, respectively [72]. In a retrospective series, no advantage in local control was present when radiation therapy was added to surgical excision for local failure in patients with previous excision and radiation therapy [73]. Instead re-irradiation caused excess of complications. In the treatment of locally recurrent disease, amputation rates are approximately twice that of primary disease in the tumors of the extremities and limb-girdle, 22 percent to 25 percent [72, 74]. Aggressive surgical treatment of local recurrences would seem to be justified in the light of relatively good results achieved after adequate treatment of local recurrence. Isolated limb perfusion with melphalan may enable limb-sparing surgery in some selected cases [75, 76].

1.6 Prognosis and Prognostic Factors

Indications of the quality of the treatment of STS are overall survival, local control and functional outcome. Strongest prognostic factors for local recurrence are surgical margin and age of the patient (Table 1). In two series [10, 77] time of treatment has remained statistically significant in multivariate analysis possibly indicating some changes in the natural course of STS during last decades. Recurrent disease at presentation has a negative prognostic value on local control in some series [7, 78] whereas local control in patients with primary and locally recurrent disease at presentation was shown to be equal after aggressive local treatment with high-class surgery in one series [38].

1.7 Treatment Guidelines at Helsinki University Hospital (HUH)

All patients referred to the multimodality group are discussed at weekly interdisciplinary meetings, and treatment is conducted according to a prospective treatment protocol, which has been followed from 1987 on. The treatment protocol includes all adult soft tissue sarcomas excluding visceral sarcomas, dermatofibrosarcoma protuberans and Kaposi sarcoma. The principles of treatment are surgery selectively combined with postoperative radiation therapy. Preoperative radiation therapy is administered to large tumors in difficult locations where even marginal surgery does not seem feasible and conservative surgery is attempted. Preoperatively patients undergo an MRI, CT or both of the primary tumor area. Histological core biopsies and fine needle aspiration are taken by means of ultrasound (in deep locations CT) targeting and, to avoid contamination with tumor cells, the biopsy track is placed so that it could be excised with the tumor at the time of definite surgery. A CT of the lungs is also performed on those patients with a high-grade tumor.

Surgical resection is the primary treatment in all cases where the tumor can be removed without major sacrifice of function. If the preoperative investigations indicate that adequate surgical margins are not achievable, surgery is aimed at marginal surgical margins followed by radiation therapy. Reoperation is recommended after intralesional surgery whenever feasible. Amputation is recommended in cases of extensive infiltration of a major nerve or vascular structures, or of a joint or bone so that even marginal resection is not feasible.

If a reoperation is not technically feasible after marginal or intralesional surgery, radiation therapy is recommended, and postoperative radiation therapy is preferred. The radiation therapy is generally delivered through two opposed individually formed fields. The target volume is defined as the involved muscle compartment in the transversal direction, with a margin of at least 5 cm longitudinally. The radiation dose is 50 Gy in 5 weeks (2 Gy/day). For microscopically or macroscopically positive surgical margins, a boost is delivered to a smaller target volume (10-20 Gy in 1-2 weeks). Boost is presently offered also for patients with marginal resection. CT-based treatment planning is used, and individual fixation methods are used for patients with extremity tumors.

Amendment to protocol was added in 1998 concerning adjuvant chemotherapy: patients under 70 years are offered adjuvant chemotherapy if the tumor malignancy grade is high (III-IV in a four-tiered scale) and the tumor fulfilled at least two of the following criteria: size > 8 cm (in synovial sarcomas 5 cm), necrosis or vascular invasion. Adjuvant chemotherapy consists of a doxorubicin-ifosfamide combination that is administered six times with three-week breaks between treatments.

The resected specimens are sent to the pathologist fresh, whole, without making any cuts on the surface, the ideal being a situation where the surgeon never sees the tumor itself. After taking necessary samples for molecular analysis, the specimens are fixated in formalin. After fixation the surfaces are painted and thereafter the specimens are dissected. The narrowest margins are measured in millimeters from the tumor sections. Samples for histological examination are also selected from those areas, where the margin is smallest on macroscopic examination. The final margin is evaluated on histological slides, and the smallest margins as well as their location are reported.

The surgical margins are defined as compartmental if an intracompartmental tumor and the whole muscle compartment are excised en bloc including the natural barriers of the compartment. The margin is defined as wide if the tumor was excised with smallest microscopic margin of at least 2.5 cm. A smaller margin is accepted, however, if it

consists of an uninvolved anatomical barrier (e.g. fascia or periosteum). If the requirements for a wide margin are not fulfilled, the margin is classified as marginal (margins less than wide) or intralesional (microscopic or macroscopic tumor left). Adequate local treatment is defined as wide surgery alone or marginal surgical margin combined with radiation therapy.

Patients undergo a regular follow-up. For high-grade sarcomas, the interval is 2 months during the first 2 years, thereafter 2 to 3 times annually, and 2 to 3 times annually for low-grade tumors. Patients undergo a chest X-ray at each visit and an MRI or CT scan of the operative area 6 months postoperatively and every 6 months up to 2 years and thereafter once annually up to five years for high-grade tumors. In low-grade tumors an MRI or CT scan of the operative area is taken annually up to 7 years and thereafter once in every 18 months up to 10 years.

1.8 Centralization of Diagnostics and Treatment and it's Effect on Prognosis

Rarity of STS, demanding surgical treatment, complex radiation therapy planning and critical evaluation of patients to receive adjuvant chemotherapy, among others, are reasons why specialized multimodality STS treatment centers have been established. The importance of centralization of diagnostics and treatment of this rare malignancy is now well established [4, 53, 85-90]. In quality-control works, shortages in all areas of diagnostics and treatment together with follow-up of soft tissue sarcoma have been published.

1.8.1 Histological Diagnosis

The Scandinavian Sarcoma Group (SSG) introduced a treatment program for STS (SSG protocol V) in 1986, and the protocol was widely adopted in Finland. Recommendation concerning referral was that all patients with deep tumors (tumors under the investing fascia or subcutaneous tumors with fascial infiltration) and patients with subcutaneous tumors larger than 5 cm should be referred to a sarcoma center before any biopsy or surgery [1, 91]. In a retrospective 1,851-patient study of the SSG Register during 1986-1997, only 63 percent of soft tissue sarcoma patients were referred to a specialized soft

tissue sarcoma team before open biopsy or surgical excision [4]. Biopsy performed in the referring hospital carried a 3 to 5-fold biopsy-related complication and error rate compared to biopsy performed in a sarcoma center [92]. In a similar study 14 years later, results were similar to the previous study with 2 to 12-fold rates [93]. Criteria were formulated in the South-East Thames Region to define optimal treatment of a mass over 5 cm in diameter situated subcutaneously or deep in soft tissue, and the treatment of all new patients with primary soft tissue sarcoma diagnosed during 1986-1992 were retrospectively compared against these criteria [87]. Of the 207 patients, only 21.3 percent fulfilled the criteria for optimal preoperative investigation and 26.1 percent had no investigations whatsoever before surgical procedure. Somewhat better results were reported in a similar setting from Rhône-Alpes region: 52 percent of patients received optimal preoperative examination and 42 percent of patients were biopsied before definite surgery [94]. Guidelines for the diagnosis and treatment of soft tissue sarcoma were developed also in the region of the Comprehensive Cancer Center North-Netherlands (CCCN) by a cooperative group for rare tumors [95]. In a retrospective review with view on how well guidelines for preoperative investigations were followed, adherence to guidelines was better in a specialized center compared to referring hospitals [95]. Specialist centers tended to treat more (lower) extremity tumors, whereas retroperitoneal, pelvic and head and neck tumors were more often treated at a district hospital [95]. This difference was at least partly explained by anatomically differently seated synovial sarcomas most often seen in younger patients, who were most likely to be referred. However, lower extremity and hip STSs had the highest referral rates universally despite of histologic subtypes [95]. Older patients were diagnosed and treated more often in non-tertiary hospitals than younger patients. As a result, concentration of diagnosis and treatment of patients with soft tissue sarcoma to specialized tumor centers was stressed [95]. Several studies have shown that patients referred to specialist centers untouched have more likely larger tumor, tumor of high-grade and deep-seated tumor [2, 4, 6, 88]. This is supposedly due to the high suspicion of malignancy considering these neoplasms [2].

Clear referral policies may result in improved referral of small, subcutaneous tumors [96]. Regarding the surprisingly high rate of cases with no preoperative diagnosis before resection, Verheijen and colleagues stated that there is still uncertainty of referral pattern

and possible malignancy of subcutaneous/soft tissue tumors [32]. Therefore, Verheijen et al state that special attention should be concentrated on everyday practice-suitable guidelines adding the awareness of STS in order to lower the amount of preoperatively non-diagnosed cases from 31 percent in their study [32].

Pathologist's experience has been proposed to be crucial for correct histopathological diagnosis. In a single-institution review, 37 percent of diagnoses were corrected: in two cases from benign to sarcoma, and grade of malignancy was corrected in 25 percent of cases [45]. Of the 55 cases regarded as marginal or wide excision by the referring surgeon, in 82 percent of samples margins were positive and in 53 percent of re-excisions residual tumor was present. Lehnhardt and colleagues found concordance with the primary diagnosis on second evaluation increasing when comparing private clinic pathologists, hospital pathologists, university hospital pathologists and sarcoma specialist center pathologists [97]. The definite diagnosis was improved in 73.1 percent of cases, whereas second opinion was false in 2.5 percent of the cases [97]. Lurkin and colleagues observed similar results: over 45 percent of initial diagnoses were either completely or partially discordant with the expert opinion [98]. However, the main cause of non-concordant diagnosis was the absence of grading. If, however, the non-expert pathologist graded the tumor, the diagnosis was usually concordant with the definitive diagnosis [98]. Hence, a second expert opinion seems to be significantly important for verifying the right diagnosis.

Experience of the pathologist is pronounced with intermediate-grade or high-grade tumors and rare histological subtypes, or subtypes with complexities in diagnosis. These initial diagnoses are the most frequently corrected ones on second review [97, 98]. However, there is also indications that low-grade sarcomas are actually more challenging to grade histologically than high-grade tumors [34]. Increasing incidence of a specific subtype increases the rate of correct diagnoses [97]. Diagnoses requiring more complex or newer diagnostic tools (for example molecular biology) are more frequently discordant with the specialist diagnosis. This, also, indicates the need of a second opinion in soft-tissue sarcoma diagnostics [98]. Shortages in reporting all the necessary parameters in pathology report are also reported. Grade of the tumor wasn't reported in 43.3 percent of

the histology reports in the South-East Thames Region [87]. Reports seem to be more complete in a specialist center where both tumor size and depth were more frequently recorded when comparing to a district hospital [90, 95].

1.8.2 Preoperative Imaging

Rates of preoperative imaging of the primary tumor by MRI or CT were 80 percent and 35 percent for patients primarily treated at a sarcoma center and patients primarily treated elsewhere, respectively [4]. In another paper, attending specialist had a significant effect on preoperative investigations (CT or MRI of the primary tumor site and chest CT) and referral to adjuvant therapy [87]. In Finland, patients with definite diagnosis of STS were more likely to undergo appropriate preoperative investigations in "high-volume centers" [90]. Quality-control study from two French regions showed that only 37 percent of subcutaneous tumors were adequately imaged before surgery [3].

1.8.3 Quality of Surgery and Adjuvant Treatment

In their 1986-92-series, Clasby and colleagues observed substantial deficiencies in adequate local treatment compared to treatment protocol: only 60 percent of patients received adequate surgical treatment. In a Swedish patient series, wide margin was achieved in 11 percent and 66 percent of patients operated in local hospitals and at a sarcoma center, respectively. In the same report, cumulative local recurrence rate was 0.20 at five years among patients operated for primary sarcoma at a specialized sarcoma center and 0.70 for patients treated by surgery outside a sarcoma center [4]. An earlier population-based series from Sweden showed local recurrence rates of 18, 24 and 45 percent for patients referred to a sarcoma treating team untouched, after surgery or not referred at all [88]. In the USA in a population-based sample study in 2002 researchers concluded that treatment of soft tissue sarcoma of the extremity best followed existing recommendations [5]. Age at diagnosis was strongly related to treatment and outcome [5].

Completeness of the initial surgical procedure is often exaggerated when performed at a local hospital. Residual tumor was found in 31 percent and 91 pe cent of reresections of

patients referred for complete resection of the tumor [52, 61, 89]. Wide, marginal and intralesional surgical margins were achieved in first surgical procedure in 44 percent, 30 percent and 26 percent of cases, respectively [87]. Of the patients not having wide surgical margin, only 48 percent received postoperative radiation therapy as recommended by the guidelines [87]. Adherence to treatment protocol is shown to be firmer at a specialized sarcoma center with higher volume of patients: Wide margin was more often reached and adjuvant therapy given with patients undergone inadequate surgery in higher-volume centers [4, 90]. Patients referred to specialist centers preoperatively have fewer operations than those referred postoperatively (1.7 times more operations) or not referred at all (1.4 times more operations) [4]. This is largely due to additional operations aiming for wide margins. In a 2009 paper, Gadgeel and colleagues showed that treatment patterns of STS follow treatment guidelines rather well with extremity tumors, but with gynecological tumors and tumors at other sites, patterns are more variable [5]. For example, of patients with tumor of other site, 56 percent with positive margins received only resection. Patients with STS of the extremity were the most likely to receive RT. The use of RT increased with higher-grade tumors, whereas surgical margin and tumor depth didn't have an effect on the use of RT. Chemotherapy was used more often with higher-stage diseases and poor differentiation of the tumor tissue. In addition, in extremity sarcomas, chemotherapy was used more commonly with increasing tumor depth, grade and RT [5].

Treatment guidelines of STS don't usually specify treatment between different age groups. However, referral to specialist centers seems to linearly decrease with increasing patient age [95]. In addition, elderly patients (i.e. patients over 70 years of age) with high-grade STS of the extremity received radiation therapy less often (69.6 percent) than patients aged 50 to 70 (74.9 percent) and under 50 (78.3 percent) [99]. The difference retained its significance in multivariate analysis when comparing patients under 50 years of age and those over 70. Furthermore, patients not receiving RT had shorter overall survival rates, and over 70 years old patients not receiving RT had shorter disease-specific survival rates compared to patients under 50 years of age receiving chemotherapy. This result indicates that elderly patients might also benefit from receiving RT [99]. On the other hand, Gadgeel and colleagues observed the opposite: increasing age was associated with more radiotherapy in STSs of the extremities [5]. However, they had stratified the cohort in groups consisting of patients under and over 50 years of age [5].

1.8.4 Survival

In general, treatment centralization shows an inverse effect on short-term mortality, largely because of high-volume treatment centers having high-volume surgeons specialised in a particular operation. Furthermore, patients treated at low-volume centers have a higher probability to be operated by a low-volume surgeon [100]. Gustafson and colleagues observed in their paper that better results in STS center was due to better-quality surgery, whereas amputation rate and use of adjuvant radiation therapy were similar compared to patients not treated in the center [88]. Contradictory results are also reported: patients treated at high-volume centers had lower amputation rates compared to low-volume centers in a registry-based series [6]. High-volume centers show higher recurrence-free rates than low-volume centers [2, 4, 77, 88, 90]. Local recurrence occurred in 26.8 percent of patients and distant relapse in 14.6 percent in the London series [87]. In another health region in the UK, treatment in a sarcoma center yielded local recurrence-rate of 19 percent and treatment in district general hospital 39 percent [2].

There is a little evidence on centralization having a positive effect on overall survival. Bhangu and colleagues showed that patients diagnosed with stage III tumors had slightly better prognosis when treated at a specialist center compared to district hospital [2]. Gutierrez and colleagues found in their study on 4,205 patients from the Florida Cancer Data System that treatment at a high-volume center had an independent positive prognostic value [6]. Short-term survival (i.e. 30-day and 90-day mortality) was better with patients treated at high-volume centers compared to low-volume centers [6]. Median overall survival was 40 months compared to 37, and the difference was even more pronounced with high-grade tumors, tumors over 10 cm in diameter, and truncal and retroperitoneal tumors [6]. Similar trend was also seen in head and neck and extremity tumors, although the difference was not statistically significant [6]. The conclusions included that patients with tumors exceeding 10 cm, with high-grade tumors, and with truncal or retroperitoneal sarcomas should be exclusively treated at a high-volume center [6].

There have been indications that adherence to treatment protocol has increased by time. In a 2017-cohort study comparing STSs treated in Finland during 1998-2001 and 2005-2010, Sampo and colleagues noticed that in patients referred to specialized treatment centers, larger part of tumors were referred untouched during the latter period [77, 90]. Further, patients had fewer operations, larger portion of tumors were resected with a wide definite margin, and those patients with inadequate margin received adjuvant radiotherapy more often in the 2005-2010 cohort [77, 90]. In a 1,851-patient study, referral practice improved from 1986-1988 period to 1995-1997 period, and the improvement applied especially to deep-seated tumors [4]. Furthermore, between these cohorts the amputation rate decreased from 15 percent to 9 percent [4]. Rydholm and colleagues observed similar results in a 1970-1981 series [101]. In addition, they made an observation that counties more distant from sarcoma center had similar referral pattern, delayed by about five years [1]. Somewhat worrisome is the fact present in the 2-region French series that although overall most cases were discussed at a multisidciplinary meeting at some point of the treatment (80.7 percent), only 6.4 percent were discussed before biopsy and only 29.9 percent before surgery [3].

2 Aims of the Study

The main aim of the present study was to report treatment and survival rates of patients treated by the multidisciplinary Soft Tissue Sarcoma Group at Helsinki University Hospital during its first 25 years. Special interest was in 1) adherence to treatment protocol, 2) metastases-free survival (MFS) and overall survival (OS) over time, and 3) treatment and survival of patients referred for radiation-associated soft tissue sarcoma. The present study works as a quality control work.

3 Materials and Methods

The patient series consists of the soft tissue sarcoma patients treated by the Soft Tissue Sarcoma Group at HUH during 1987-2012. Treatment was planned and executed according to the group's prospective treatment protocol set up in 1987 based on Scandinavian Sarcoma Group recommendations. LC, MFS, OS and sarcoma-specific survival (SSS) were calculated according to the Kaplan-Meier method. Differences in survival rates of different subgroups were analyzed with the log rank test for discrete variables and with Cox regression analysis for continuous variables. The $\chi 2$ test was used to assess differences in the distribution of tumor characteristics among groups. IBM® SPSS® Statistics version 23 (SPSS, Chicago, Illinois, USA) was used for all analyses.

4 Results

A total of 1,327 patients with definite diagnosis of STS were treated during 1987-2012 (Tables 2a and 2b). The most common presentation status was primary tumor without metastases (79 percent) whereas 13 percent of patients were referred for metastatic disease. Of the 1,182 patients referred for a primary tumor only 411 (35 percent) were referred untouched. The proportion increased from 13 percent to 47 percent by time, $p < 0.0001$. Median follow-up for the surviving patients was 6.3 years.

Of the 1,115 patients treated with curative intent, 680 (61 percent) patients underwent only one surgical procedure, and the percentage increased over time. Five patients with extraskeletal Ewing/PNET had radiation therapy only as local treatment. Wide margin was reached in 381 patients. Four hundred ninety-three patients received adjuvant radiation therapy and 197 patients received adjuvant chemotherapy. Of the 136 patients with definite intralesional margin, 87 (64 percent) received radiation therapy. Of the 593 patients with definite marginal margin, 367 (62 percent) received radiation therapy.

4.1 Patients Referred for Radiation-associated Sarcoma

Fifty-nine patients were referred for a radiation-associated sarcoma (Tables 3 and 4). Most of these (77 percent) appeared in a radiation field of an invasive breast cancer (BC) patient. Fifty-two of the 59 patients received treatment with curative intent. Thirty-eight percent had operation with wide margin whereas intralesional operation was the definite margin in 5 patients. Re-irradiation was used in 7 (13 percent) patients and 4 patients received chemotherapy. Local control was 73 percent and 58 percent at 5 and 10 years, respectively, in the 52 patients receiving treatment with curative intention.

4.2 Patients Treated with Palliative Intention

Two hundred twelve patients had palliative treatment. One hundred and two (48 percent) received palliative chemotherapy. Doxorubicine alone or combined with ifosfamide was the most common treatment choice for first line. Percentage of patients receiving palliative chemotherapy remained stable over time. One-year and three-year survival for all patients with palliative treatment was 52 percent and 17 percent, respectively. Median survival was 1 year with no improvement over time, Fig.1, $p = 0.13$.

4.3 Survival

For all patients with curative intention, 5- and 10-year overall survival was 68 percent and 55 percent, respectively, Fig. 2, with no improvement over time. For patients with radiation-associated sarcoma receiving curative treatment ($n = 52$) 5- and 10-year OS was 63 percent and 60 percent, respectively, Fig.3.

5 Discussion and Conclusions

In this retrospective quality control study on soft tissue sarcoma patients treated during 1987-2012 by the soft tissue sarcoma group at Helsinki University Hospital, we recorded no improvement in local control or overall survival. However, larger percentage of patients had adequate preoperative investigations and was treated with single operation. Still, approximately one third of patients did not receive adjuvant radiation therapy after marginal surgery. The proportion of patients with tumor of the extremities or trunk wall receiving inadequate local therapy according to treatment protocol in our first report was 40 percent [53]. Since the first report we followed the protocol more firmly and managed to reduce the proportion of patients receiving inadequate treatment markedly: in the next report on patients treated 1987-1997, 22 percent of patients received inadequate local treatment [38]. However, the present series consists of patients wih tumor in any site of the body. Reporting local treatment characteristics of all patients in the present series was beyond the scope. Adherence to treatment protocol should be emphasized and any exception should be systematically and prospectively recorded to enable future quality assurance. Low adherence to proposed treatment protocols is shown in many studies [4, 87, 94]. Possible explanations to suboptimal local treatment are low grade tumor and expected low local recurrence rate. Many patients with advanced age have poor physical condition with many illnesses and are not candidates for extensive resection and possible reconstruction surgery. Radiation therapy with 25 doses also is a challenging treatment modality for a patient. Horton and colleagues pointed out that elderly patients are more likely not to receive radiation therapy whereas they have increased cancer-related morbidity and mortality after adjusting for demographic and tumor factors [99]. Furthermore, some people refuse mutilating amputation required to achieve marginal margin and are operated with intralesional limb-salvage surgery. Reasons for not offering adjuvant radiation therapy were not systematically recorded in patient files. Suboptimal local treatment in STS is a widely published area. Percentage of patients with inadequate margins and who received adjuvant radiation therapy was below 50 percent in two regional studies and in one database review [4, 87, 94]. It is noticeable that only in a dismal proportion of cases radiation therapy is omitted because of patient-related causes. Merely age should not form the basis for decision on sarcoma treatment [95]. More importantly, physical condition and wish of the patient should be considered.

Approximately one tenth of patients in the present series were referred for locally recurrent disease with or without systemic disease. Previous local treatment for primary tumor, surgery with or without radiation therapy, makes the operation conditions more difficult based on changed anatomy and scarring. It is thus also more difficult to achieve adequate local control [71]. However, recurrent disease at presentation had no adverse prognostic value on further local recurrence with aggressive local treatment in our study [38] contradicting the results by Pisters et al [7]. Locally recurrent disease is treated according to the same principles as primary tumors in the protocol set up at our institution in 1987. Prior surgery changes anatomy and makes further surgery more challenging which calls for surgeon´s skills and experience.

One special challenge for soft tissue sarcoma treatment team is radiation-associated sarcoma which had a hazard ratio of nearly ten for local recurrence in our series on patients treated 1987-1997 [38]. Most RAS nowadays are located axially after treatment for breast cancer. Number of radiation-associated sarcomas was small but showed some trend of increase. In fact, we have shown that in a series based on Finnish Cancer registry the first RAS AS was diagnosed in a patient treated for BC in 1984 [25]. Thereafter the incidence of AS steadily increased and, in fact, AS was the most common RAS histologic subtype also in the current series. Literature reveals few cases of secondary in-field AS occurring after RT for BC in the 1970s and having a latency period of 2.5-17 years [102-111]. In a series of five patients with RAS treated during 1953-1968 for BC there was no AS [112]. Instead, most secondary AS cases are described after RT for BC occurring in patients treated in the 1980s or later [113]. In the latest study on patients from Surveillance, Epidemiology, and End Results (SEER) database with RAS after RT to BC during 1973-2003, AS was strongly associated with breast-conserving surgery even after adjusting for RT and axillary evacuation [114]. Mastectomy is the preferred choice of treatment for RAS AS after breast-conserving surgery [25]. Because of previous radiation therapy surgery is in most cases the only treatment modality. However, in case of long latency period re-irradiation may be feasible. With aggressive local treatment (usually mastectomy) of RAS similar local control rate can be achieved compared to patients treated for sporadic tumor [25]. In the present study we demonstrated 5- and 10-year OS of 63 percent and 60 percent in patients with RAS receiving curative treatment. It is noticeable that the present series includes RAS of all locations.

Most soft tissue sarcoma patients are elderly and at considerable risk of developing life-threatening or fatal side-effects like neutropenic infections. Therefore, expected benefit from palliative treatment of locally advanced or systemic disease should be carefully weighted against adverse effects. The overall 5-year survival of patients with metastatic soft-tissue sarcoma is poor with a median survival of 12-17 months [10, 12, 115]. Few patients having complete resection of all nodules with negative margins may be even cured [116] but the benefit of surgery has been questioned because of selection bias [117].

Few effective chemotherapy regimens for metastatic STS exist. Doxorubicin is the most important drug providing a median survival of only approximately one year [118]. In a 2,281-patient meta-analysis of eight RCTs, Bramwell and colleagues detected a higher tumor response rate with combination chemotherapy compared with single-agent doxorubicin but the increase did not confer to improved survival in one or two years [118]. Although not systematically reported, adverse effects seemed to be reported more commonly with combination chemotherapy. With some patients, palliative radiation therapy or even curative stereotactic radiation therapy is possible. Given the frailty of many patients best supportive care may the most ideal approach. In the present series, only approximately half of the patients with no possibility of curative treatment at referral received palliative chemotherapy. Studying treatment or survival in patients of locally advanced or systemic disease developing after curative treatment was beyond the scope of the present study.

Our study has certain limitations. During 30 years time of data collection, reporting of data has changed. However, one of the strengths of the study include a consistent written treatment protocol with the same policy of local treatment starting 1987 and with adjuvant chemotherapy starting 1998. Few new drugs for locally advanced or systemic sarcoma were introduced but they usually are indicated for only a small highly selected patient population.

In conclusion, the present series emphasizes the importance of multimodality treatment team and written treatment protocol. To ascertain one aspect of high-quality treatment, any exceptions from the protocol should be thoroughly discussed and reported in patient

files. To increase the percentage of patients referred for primary tumor without preceding biopsy, increasing sarcoma knowledge in district hospitals is vital.

References

1.Rydholm A: Management of patients with soft-tissue tumors. Strategy developed at a regional oncology center. Acta Orthop Scand Suppl 1983;203:13-77.

2.Bhangu AA, Beard JA, Grimer RJ: Should Soft Tissue Sarcomas be Treated at a Specialist Centre? Sarcoma 2004;8:1-6.

3.Mathoulin-Pelissier S, Chevreau C, Bellera C, et al.: Adherence to consensus-based diagnosis and treatment guidelines in adult soft-tissue sarcoma patients: a French prospective population-based study. Ann Oncol 2014;25:225-231.

4.Bauer HC, Trovik CS, Alvegard TA, et al.: Monitoring referral and treatment in soft tissue sarcoma: study based on 1,851 patients from the Scandinavian Sarcoma Group Register. Acta Orthop Scand 2001;72:150-159.

5.Gadgeel SM, Harlan LC, Zeruto CA, et al.: Patterns of care in a population-based sample of soft tissue sarcoma patients in the United States. Cancer 2009;115:2744-2754.

6.Gutierrez JC, Perez EA, Moffat FL, et al.: Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients. Ann Surg 2007;245:952-958.

7.Pisters PW, Leung DH, Woodruff J, et al.: Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1996;14:1679-1689.

8.Fletcher CDM, World Health Organization., International Agency for Research on Cancer., *WHO classification of tumours of soft tissue and bone*. 4th ed. World Health Organization classification of tumours. 2013, Lyon: IARC Press. 468 p.

9.Zagars GK, Ballo MT, Pisters PW, et al.: Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 225 patients. Cancer 2003;97:2530-2543.

10.Gronchi A, Miceli R, Colombo C, et al.: Primary extremity soft tissue sarcomas: outcome improvement over time at a single institution. Ann Oncol 2011;22:1675-1681.

11.Potter DA, Glenn J, Kinsella T, et al.: Patterns of recurrence in patients with high-grade soft-tissue sarcomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1985;3:353-366.

12.Billingsley KG, Burt ME, Jara E, et al.: Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229:602-610; discussion 610-602.

13.Gadd MA, Casper ES, Woodruff JM, et al.: Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Annals of Surgery 1993;218:705-712.

14.Al-Refaie WB, Andtbacka RH, Ensor J, et al.: Lymphadenectomy for isolated lymph node metastasis from extremity soft-tissue sarcomas. Cancer 2008;112:1821-1826.

15.Atalay C, Altinok M, Seref B: The impact of lymph node metastases on survival in extremity soft tissue sarcomas. World J Surg 2007;31:1433-1437.

16.Fong Y, Coit DG, Woodruff JM, Brennan MF: Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Annals of Surgery 1993;217:72-77.

17.Stojadinovic A, Leung DH, Hoos A, et al.: Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. Ann Surg 2002;235:424-434.

18.Cahan WG, Woodard HQ, Higinbotham NL, et al.: Sarcoma arising in irradiated bone: report of eleven cases. 1948. Cancer 1998;82:8-34.

19.Arlen M, Higinbotham NL, Huvos AG, et al.: Radiation-induced sarcoma of bone. Cancer 1971;28:1087-1099.

20.Kalra S, Grimer RJ, Spooner D, et al.: Radiation-induced sarcomas of bone: factors that affect outcome. J Bone Joint Surg Br 2007;89:808-813.

21.Erel E, Vlachou E, Athanasiadou M, et al.: Management of radiation-induced sarcomas in a tertiary referral centre: a review of 25 cases. Breast 2010;19:424-427.

22.Kirova YM, Vilcoq JR, Asselain B, et al.: Radiation-induced sarcomas after radiotherapy for breast carcinoma: a large-scale single-institution review. Cancer 2005;104:856-863.

23.Mavrogenis AF, Pala E, Guerra G, Ruggieri P: Post-radiation sarcomas. Clinical outcome of 52 Patients. J Surg Oncol 2012;105:570-576.

24.Kim KS, Chang JH, Choi N, et al.: Radiation-Induced Sarcoma: A 15-Year Experience in a Single Large Tertiary Referral Center. Cancer Res Treat 2016;48:650-657.

25.Salminen SH, Sampo MM, Bohling TO, et al.: Radiation-associated sarcoma after breast cancer in a nationwide population: Increasing risk of angiosarcoma. Cancer Med 2018;7:4825-4835.

26.Wiklund TA, Blomqvist CP, Raty J, et al.: Postirradiation sarcoma. Analysis of a nationwide cancer registry material. Cancer 1991;68:524-531.

27.Adams SC, Potter BK, Pitcher DJ, Temple HT: Office-based core needle biopsy of bone and soft tissue malignancies: an accurate alternative to open biopsy with infrequent complications. Clin Orthop Relat Res 2010;468:2774-2780.

28.Hasegawa T, Yamamoto S, Nojima T, et al.: Validity and reproducibility of histologic diagnosis and grading for adult soft-tissue sarcomas. Hum Pathol 2002;33:111-115.

29.Hoeber I, Spillane AJ, Fisher C, Thomas JM: Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors. Annals of Surgical Oncology : The Official Journal of the Society of Surgical Oncology 2001;8:80-87.

30.Mitsuyoshi G, Naito N, Kawai A, et al.: Accurate diagnosis of musculoskeletal lesions by core needle biopsy. J Surg Oncol 2006;94:21-27.

31.Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF: Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 1997;4:425-431.

32.Verheijen P, Witjes H, van Gorp J, et al.: Current pathology work-up of extremity soft tissue sarcomas, evaluation of the validity of different techniques. Eur J Surg Oncol 2010;36:95-99.

33.Strauss DC, Qureshi YA, Hayes AJ, et al.: The role of core needle biopsy in the diagnosis of suspected soft tissue tumours. J Surg Oncol 2010;102:523-529.

34.Ray-Coquard I, Ranchere-Vince D, Thiesse P, et al.: Evaluation of core needle biopsy as a substitute to open biopsy in the diagnosis of soft-tissue masses. Eur J Cancer 2003;39:2021-2025.

35.Enneking WF, Spanier SS, Malawer MM: The effect of the Anatomic setting on the results of surgical procedures for soft parts sarcoma of the thigh. Cancer 1981;47:1005-1022.

36.Yang JC, Chang AE, Baker AR, et al.: Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1998;16:197-203.

37.O'Sullivan B, Davis AM, Turcotte R, et al.: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002;359:2235-2241.

38.Sampo M, Tarkkanen M, Huuhtanen R, et al.: Impact of the smallest surgical margin on local control in soft tissue sarcoma. The British journal of surgery 2008;95:237-243.

39.Karakousis CP, Emrich LJ, Rao U, Khalil M: Limb salvage in soft tissue sarcomas with selective combination of modalities. European journal of surgical oncology : the

journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 1991;17:71-80.

40.Khanfir K, Alzieu L, Terrier P, et al.: Does adjuvant radiation therapy increase loco-regional control after optimal resection of soft-tissue sarcoma of the extremities? Eur J Cancer 2003;39:1872-1880.

41.McKee MD, Liu DF, Brooks JJ, et al.: The prognostic significance of margin width for extremity and trunk sarcoma. Journal of surgical oncology 2004;85:68-76.

42.Jebsen NL, Trovik CS, Bauer HC, et al.: Radiotherapy to improve local control regardless of surgical margin and malignancy grade in extremity and trunk wall soft tissue sarcoma: a Scandinavian sarcoma group study. Int J Radiat Oncol Biol Phys 2008;71:1196-1203.

43.Lewis JJ, Leung D, Espat J, et al.: Effect of reresection in extremity soft tissue sarcoma. Annals of Surgery 2000;231:655-663.

44.Pisters PW, Harrison LB, Leung DH, et al.: Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1996;14:859-868.

45.Randall RL, Bruckner JD, Papenhausen MD, et al.: Errors in diagnosis and margin determination of soft-tissue sarcomas initially treated at non-tertiary centers. Orthopedics 2004;27:209-212.

46.Sadoski C, Suit HD, Rosenberg A, et al.: Preoperative radiation, surgical margins, and local control of extremity sarcomas of soft tissues. Journal of surgical oncology 1993;52:223-230.

47.Dickinson IC, Whitwell DJ, Battistuta D, et al.: Surgical margin and its influence on survival in soft tissue sarcoma. ANZ Journal of Surgery 2006;76:104-109.

48.Baldini EH, Goldberg J, Jenner C, et al.: Long-term outcomes after function-sparing surgery without radiotherapy for soft tissue sarcoma of the extremities and trunk. J Clin Oncol 1999;17:3252-3259.

49.Rydholm A, Gustafson P, Rooser B, et al.: Limb-sparing surgery without radiotherapy based on anatomic location of soft tissue sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1991;9:1757-1765.

50.Pisters PW, Pollock RE, Lewis VO, et al.: Long-term results of prospective trial of surgery alone with selective use of radiation for patients with T1 extremity and trunk soft tissue sarcomas. Ann Surg 2007;246:675-681; discussion 681-672.

51.Chandrasekar CR, Wafa H, Grimer RJ, et al.: The effect of an unplanned excision of a soft-tissue sarcoma on prognosis. J Bone Joint Surg Br 2008;90:203-208.
52.Zagars GK, Ballo MT, Pisters PW, et al.: Surgical margins and reresection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. Cancer 2003;97:2544-2553.
53.Wiklund T, Huuhtanen R, Blomqvist C, et al.: The importance of a multidisciplinary group in the treatment of soft tissue sarcomas. Eur J Cancer 1996;32A:269-273.
54.Demetri GD, Pollock R, Baker L, et al.: NCCN sarcoma practice guidelines. National Comprehensive Cancer Network. Oncology (Williston Park) 1998;12:183-218.
55.Pisters PW: Combined modality treatment of extremity soft tissue sarcomas. Annals of Surgical Oncology : The Official Journal of the Society of Surgical Oncology 1998;5:464-472.
56.Choong PF, Petersen IA, Nascimento AG, Sim FH: Is radiotherapy important for low-grade soft tissue sarcoma of the extremity? Clin Orthop Relat Res 2001;387:191-199.
57.Trovik CS, Bauer HC, Berlin O, et al.: Local recurrence of deep-seated, high-grade, soft tissue sarcoma: 459 patients from the Scandinavian Sarcoma Group Register. Acta Orthopaedica Scandinavica 2001;72:160-166.
58.Stefanovski PD, Bidoli E, De Paoli A, et al.: Prognostic factors in soft tissue sarcomas: a study of 395 patients. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2002;28:153-164.
59.Al-Refaie WB, Habermann EB, Jensen EH, et al.: Surgery alone is adequate treatment for early stage soft tissue sarcoma of the extremity. Br J Surg 2010;97:707-713.
60.ESMO: Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii102-112.
61.Rehders A, Stoecklein NH, Poremba C, et al.: Reexcision of soft tissue sarcoma: sufficient local control but increased rate of metastasis. World J Surg 2009;33:2599-2605.
62.Fiore M, Casali PG, Miceli R, et al.: Prognostic effect of re-excision in adult soft tissue sarcoma of the extremity. Ann Surg Oncol 2006;13:110-117.
63.Alektiar KM, Velasco J, Zelefsky MJ, et al.: Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. International journal of radiation oncology, biology, physics 2000;48:1051-1058.

64.Herbert SH, Corn BW, Solin LJ, et al.: Limb-preserving treatment for soft tissue sarcomas of the extremities. The significance of surgical margins. Cancer 1993;72:1230-1238.

65.Cahlon O, Spierer M, Brennan MF, et al.: Long-term outcomes in extremity soft tissue sarcoma after a pathologically negative re-resection and without radiotherapy. Cancer 2008;112:2774-2779.

66.Kim YB, Shin KH, Seong J, et al.: Clinical significance of margin status in postoperative radiotherapy for extremity and truncal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 2008;70:139-144.

67.Delaney TF, Kepka L, Goldberg SI, et al.: Radiation therapy for control of soft-tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys 2007;67:1460-1469.

68.Pervaiz N, Colterjohn N, Farrokhyar F, et al.: A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573-581.

69.Gortzak E, Azzarelli A, Buesa J, et al.: A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer 2001;37:1096-1103.

70.Verma S, Younus J, Stys-Norman D, et al.: Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma. Cancer Treat Rev 2008;34:339-347.

71.Robinson M, Barr L, Fisher C, et al.: Treatment of extremity soft tissue sarcomas with surgery and radiotherapy. Radiother Oncol 1990;18:221-233.

72.Midis GP, Pollock RE, Chen NP, et al.: Locally recurrent soft tissue sarcoma of the extremities. Surgery 1998;123:666-671.

73.Torres MA, Ballo MT, Butler CE, et al.: Management of locally recurrent soft-tissue sarcoma after prior surgery and radiation therapy. Int J Radiat Oncol Biol Phys 2007;67:1124-1129.

74.Trovik CS, Gustafson P, Bauer HC, et al.: Consequences of local recurrence of soft tissue sarcoma: 205 patients from the Scandinavian Sarcoma Group Register. Acta Orthopaedica Scandinavica 2000;71:488-495.

75.Thijssens KM, van Ginkel RJ, Pras E, et al.: Isolated limb perfusion with tumor necrosis factor alpha and melphalan for locally advanced soft tissue sarcoma: the value of adjuvant radiotherapy. Annals of Surgical Oncology : The Official Journal of the Society of Surgical Oncology 2006;13:518-524.

76.Grunhagen DJ, de Wilt JH, Graveland WJ, et al.: Outcome and prognostic factor analysis of 217 consecutive isolated limb perfusions with tumor necrosis factor-alpha and melphalan for limb-threatening soft tissue sarcoma. Cancer 2006;106:1776-1784.

77.Sampo MM, Klintrup K, Tukiainen EJ, et al.: Improved prognosis in soft-tissue sarcoma of extremity and trunk wall. Acta Orthop 2017;88:116-120.

78.Gronchi A, Casali PG, Mariani L, et al.: Status of surgical margins and prognosis in adult soft tissue sarcomas of the extremities: a series of patients treated at a single institution. J Clin Oncol 2005;23:96-104.

79.Eilber FC, Rosen G, Nelson SD, et al.: High-grade extremity soft tissue sarcomas: factors predictive of local recurrence and its effect on morbidity and mortality. Ann Surg 2003;237:218-226.

80.Vraa S, Keller J, Nielsen OS, et al.: Prognostic factors in soft tissue sarcomas: the Aarhus experience. European journal of cancer 1998;34:1876-1882.

81.Lewis JJ, Leung D, Heslin M, et al.: Association of local recurrence with subsequent survival in extremity soft tissue sarcoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1997;15:646-652.

82.Gronchi A, Lo Vullo S, Colombo C, et al.: Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg 2010;251:506-511.

83.Trovik CS, Bauer HC, Alvegard TA, et al.: Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register. European journal of cancer 2000;36:710-716.

84.Stoeckle E, Gardet H, Coindre JM, et al.: Prospective evaluation of quality of surgery in soft tissue sarcoma. Eur J Surg Oncol 2006;32:1242-1248.

85.Grohn P, Heinonen E, Santavirta S, et al.: The management of soft tissue sarcomas. Duodecim; laaketieteellinen aikakauskirja 1979;95:1301-1306.

86.Rantakokko V, Ekfors TO: Sarcomas of the soft tissues in the extremities and limb girdles. Analysis of 240 cases diagnosed in Finland in 1960--1969. Acta Chir Scand 1979;145:384-394.

87.Clasby R, Tilling K, Smith MA, Fletcher CD: Variable management of soft tissue sarcoma: regional audit with implications for specialist care. The British journal of surgery 1997;84:1692-1696.

88.Gustafson P, Dreinhofer KE, Rydholm A: Soft tissue sarcoma should be treated at a tumor center. A comparison of quality of surgery in 375 patients. Acta Orthopaedica Scandinavica 1994;65:47-50.

89.Karakousis CP, Proimakis C, Walsh DL: Primary soft tissue sarcoma of the extremities in adults. The British journal of surgery 1995;82:1208-1212.

90.Sampo MM, Ronty M, Tarkkanen M, et al.: Soft tissue sarcoma - a population-based, nationwide study with special emphasis on local control. Acta Oncol 2012;51:706-712.

91.Stener B: The management of soft tissue tumors. Int Orthop 1978;1:289-298.

92.Mankin HJ, Lange TA, Spanier SS: The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Joint Surg Am 1982;64:1121-1127.

93.Mankin HJ, Mankin CJ, Simon MA: The hazards of the biopsy, revisited. Members of the Musculoskeletal Tumor Society. J Bone Joint Surg Am 1996;78:656-663.

94.Ray-Coquard I, Thiesse P, Ranchere-Vince D, et al.: Conformity to clinical practice guidelines, multidisciplinary management and outcome of treatment for soft tissue sarcomas. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO 2004;15:307-315.

95.Nijhuis PH, Schaapveld M, Otter R, Hoekstra HJ: Soft tissue sarcoma--compliance with guidelines. Cancer 2001;91:2186-2195.

96.Bauer HC, Alvegard TA, Berlin O, et al.: The Scandinavian Sarcoma Group Register 1986-2001. Acta Orthop Scand Suppl 2004;75:8-10.

97.Lehnhardt M, Daigeler A, Hauser J, et al.: The value of expert second opinion in diagnosis of soft tissue sarcomas. J Surg Oncol 2008;97:40-43.

98.Lurkin A, Ducimetiere F, Vince DR, et al.: Epidemiological evaluation of concordance between initial diagnosis and central pathology review in a comprehensive and prospective series of sarcoma patients in the Rhone-Alpes region. BMC Cancer 2010;10:150.

99.Horton JK, Gleason JF, Jr., Klepin HD, et al.: Age-related disparities in the use of radiotherapy for treatment of localized soft tissue sarcoma. Cancer 2011;

100.Birkmeyer JD, Stukel TA, Siewers AE, et al.: Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117-2127.

101.Rydholm A, Berg NO, Gullberg B, et al.: Prognosis for soft-tissue sarcoma in the locomotor system. A retrospective population-based follow-up study of 237 patients. Acta Pathol Microbiol Immunol Scand A 1984;92:375-386.

102.Maddox JC, Evans HL: Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer 1981;48:1907-1921.

103.Segal SL, Lenchner GS, Cichelli AV, et al.: Angiosarcoma presenting as diffuse alveolar hemorrhage. Chest 1988;94:214-216.

104.Hamels J, Blondiau P, Mirgaux M: Cutaneous angiosarcoma arising in a mastectomy scar after therapeutic irradiation. Bull Cancer 1981;68:353-356.

105.Otis CN, Peschel R, McKhann C, et al.: The rapid onset of cutaneous angiosarcoma after radiotherapy for breast carcinoma. Cancer 1986;57:2130-2134.

106.Davies JD, Rees GJ, Mera SL: Angiosarcoma in irradiated post-mastectomy chest wall. Histopathology 1983;7:947-956.

107.Givens SS, Ellerbroek NA, Butler JJ, et al.: Angiosarcoma arising in an irradiated breast. A case report and review of the literature. Cancer 1989;64:2214-2216.

108.Stotter AT, McNeese MD, Ames FC, et al.: Predicting the rate and extent of locoregional failure after breast conservation therapy for early breast cancer. Cancer 1989;64:2217-2225.

109.Body G, Sauvanet E, Calais G, et al.: [Cutaneous angiosarcoma of the breast following surgery and irradiation of breast adenocarcinoma]. J Gynecol Obstet Biol Reprod (Paris) 1987;16:479-483.

110.Edeiken S, Russo DP, Knecht J, et al.: Angiosarcoma after tylectomy and radiation therapy for carcinoma of the breast. Cancer 1992;70:644-647.

111.Turner WH, Greenall MJ: Sarcoma induced by radiotherapy after breast conservation surgery. Br J Surg 1991;78:1317-1318.

112.Hatfield PM, Schulz MD: Postirradiation sarcoma. Including 5 cases after X-ray therapy of breast carcinoma. Radiology 1970;96:593-602.

113.Depla AL, Scharloo-Karels CH, de Jong MAA, et al.: Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review. Eur J Cancer 2014;50:1779-1788.

114.Mery CM, George S, Bertagnolli MM, Raut CP: Secondary sarcomas after radiotherapy for breast cancer: sustained risk and poor survival. Cancer 2009;115:4055-4063.

115.Billingsley KG, Lewis JJ, Leung DH, et al.: Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer 1999;85:389-395.

116.Nevala R, Jaamaa S, Tukiainen E, et al.: Long-term results of surgical resection of lung metastases from soft tissue sarcoma: A single center experience. J Surg Oncol 2019;120:168-175.

117.Treasure T, Fiorentino F, Scarci M, et al.: Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data. BMJ Open 2012;2:

118.Bramwell VH, Anderson D, Charette ML, Sarcoma Disease Site G: Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Cochrane Database Syst Rev 2003;CD003293.

Attachments

Tables

Attachment 1

Table 1. Independent prognostic factors for local recurrence in patients with extremity or trunk wall soft tissue sarcoma [7, 10, 38, 77-84]

Authors	Years	N	Site(s)	Factors
Eilber et al. 2003	1975-1997	753	extremity	Grade, Age, Histology
Vraa et al. 1998	1979-1993	316	extremity, trunk wall	Grade, Surgical margin, Compartment, Extension of surgery, Radiation therapy
Gronchi et al. 2005	1980-2000	911	extremity	Surgical margin, Recurrent disease, Radiation therapy
Lewis et al. 1997	1982-1995	911	extremity	Age, Positive margin, Histology
Pisters et al. 1996	1982-1994	1,041	extremity	Age, Surgical margin, Recurrent disease, Histology
Gronchi et al. 2010	1985-2005	997	extremity	Surgical margin, Histology, Radiation therapy
Trovik et al. 2000	1986-1991	559	extremity, trunk wall	Surgical margin, Grade
Sampo et al. 2008	1987-2002	270	extremity, trunk wall	Surgical margin, post-irradiation sarcoma
Gronchi et al. 2011	1987-2007	1,094	extremity	Age, Surgical margin, treatment period
Stoeckle et al. 2006	1996-2002	205	extremity, trunk wall	Grade, Surgical margin
Sampo et al. 2017	1998-2001 and 2005-2010	574	extremity, trunk wall	Age, Surgical margin, treatment period

Attachment 2

Table 2a. Characteristics of all patients treated 1987-2012

	Palliative (n=212)	Curative (n=1115)	Total (N=1327)
Sex			
Male	102	569	671
Female	110	546	656
Age at Diagnosis, median (years)	58	59	59
Referral cause			
Primary without metastases	57	988	1045
Primary with metastases	112	25	137
Local recurrence without metastases	8	96	104
Local recurrence with metastases	11	2	13
Metastases	24	4	28
Primary referred (n=1182)			
Virgin	54	357	411
FNA	10	78	88
PNB	34	96	130
Open biopsy	28	77	105
Intralesional surgery	21	211	232
Marginal surgery	4	185	189
Marginal surgery+RT or Wide surgery	0	9	9
Preoperative diagnostic procedure*			
None		408	
FNA		63	
CNB		442	
Open biopsy		96	
Histologic subtype			
UPS	28	305	333
Liposarcoma	16	237	253
Leiomyosarcoma	54	178	232
Sarcoma NOS	43	70	113
Synovial sarcoma	11	81	92
Angiosarcoma	17	37	54
Fibrosarcoma	8	34	42
Extraskeletal Ewing's sarcoma/PNET	8	33	41
MPNST	9	31	40
Other spesified	18	109	127
Site			
Head&neck	14	55	69
Upper Extremity and girdle	17	181	198
Trunk wall	15	194	209
Lower Extremity and girdle	55	520	575
Deep sites	111	165	276
Grade			
Low	24	317	341
High	188	798	986
Tumour size, median (cm)*		6.8, range 0.5-50	

*in patients with primary tumor and curative treatment.

Abbreviations: FNA, fine-needle aspiration; CNB, core needle biopsy; MPNST, malignant peripheral neural sheath tumor; NOS, not otherwise spesified; PNET, primitive neuro-ectodermal tumor; RT, radiation therapy; UPS, undifferentiated pleomorphic sarcoma.

Attachment 3

Table 2b. Treatment characteristics of patients treated with curative intention 1987-2012 (N = 1115)

Number of operations	
0	5
1	682
2	307
3	18
4	3
Definite margin	
Intralesional	136
Marginal	593
Wide	381
Radiation therapy	
Yes	493
No	622
Chemotherapy	
Yes	197
No	918

Attachment 4

Table 3. Characteristics of patients referred for radiation-associated sarcoma 1987-2012

Sex	
Male	12
Female	47
Age at Diagnosis, median	62
Referral cause	
Primary without metastases	51
Primary with metastases	4
Local recurrence without metastases	4
Histologic subtype	
Angiosarcoma	19
UPS	10
Sarcoma NOS	9
Fibrosarcoma	6
Leiomyosarcoma	5
Exstraskeletal osteosarcoma	4
Myxofibrosarcoma	2
Liposarcoma	1
Epitheloid sarcoma	1
Synovial sarcoma	1
MPNST	1
Site	
Head&neck	4
Upper Extremity and girdle	6
Trunk wall	40
Lower Extremity and girdle	6
Deep sites	3
Grade	
Low	5
High	54
Tumour size, median, cm	5

Attachment 5

Table 4. Treatment characteristics of patients referred for radiation-associated sarcoma 1987-2012

Treatment intention	
Palliative	7
Curative	52
Number of operations	
0	6
1	36
2	16
3	1
Margin	
Intralesional	5
Marginal	27
Wide	20
Radiation therapy	
Yes	7
No	52
Chemotherapy	
Yes	4
No	55

Figures

Attachment 6

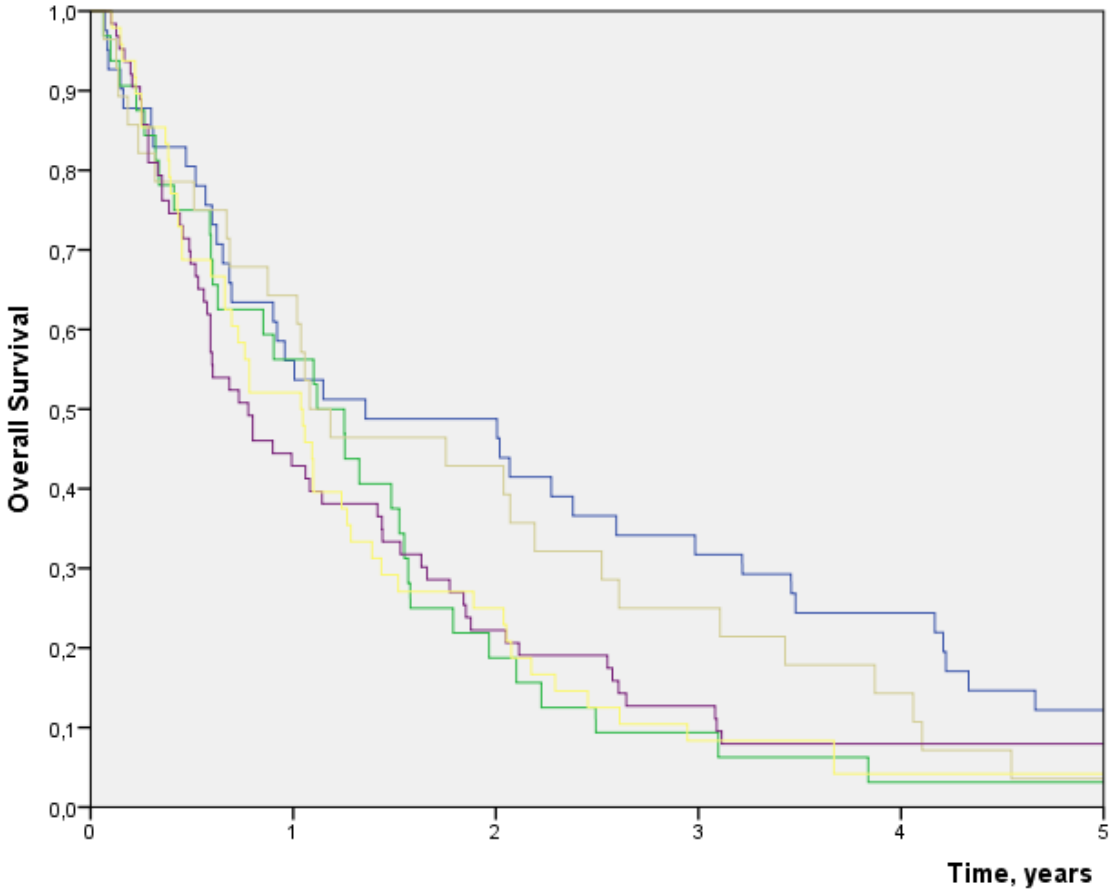

Figure 1. Overall survival by time for patients treated with palliative intent. Blue: 1987-1992. Grey: 1993-1997. Purple: 1998-2002. Yellow: 2003-2007. Green: 2008-2012.

Attachment 7

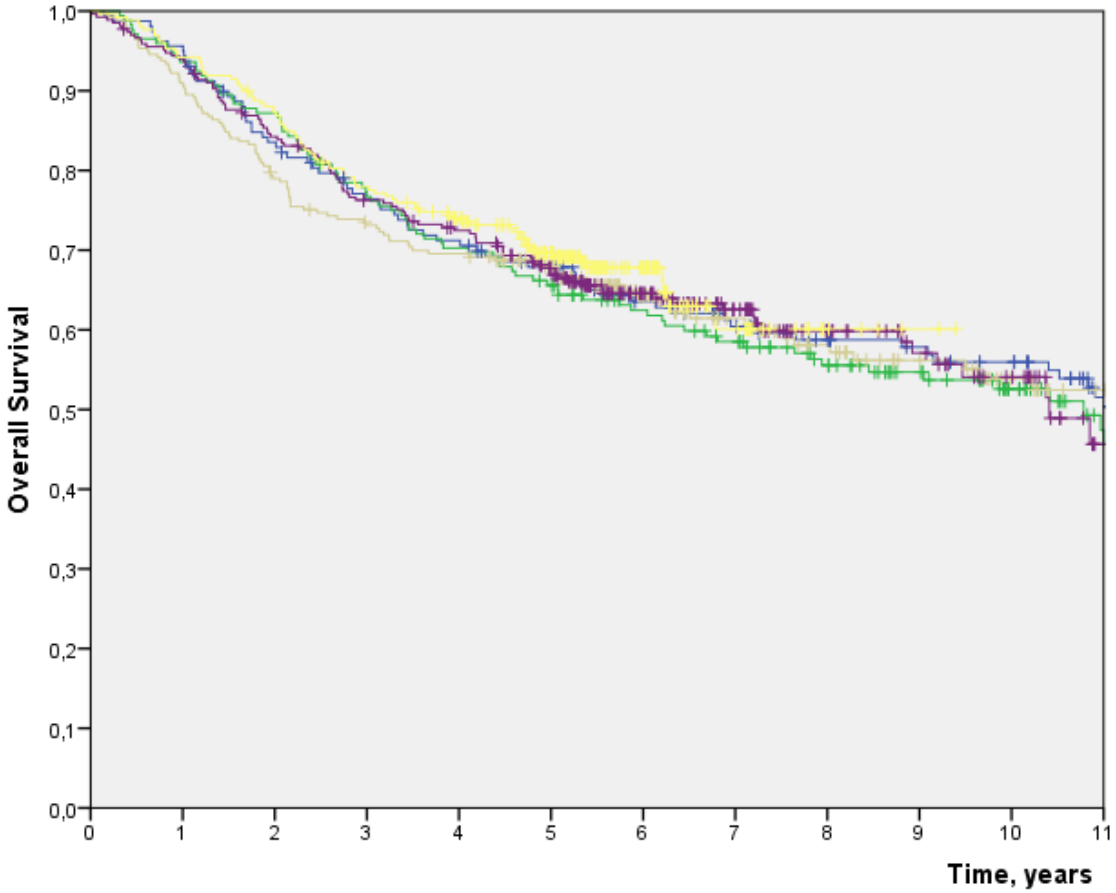

Figure 2. Overall survival by time for patients treated with curative intent. Blue: 1987-1992. Grey: 1993-1997. Purple: 1998-2002. Yellow: 2003-2007. Green: 2008-2012.

Attachment 8

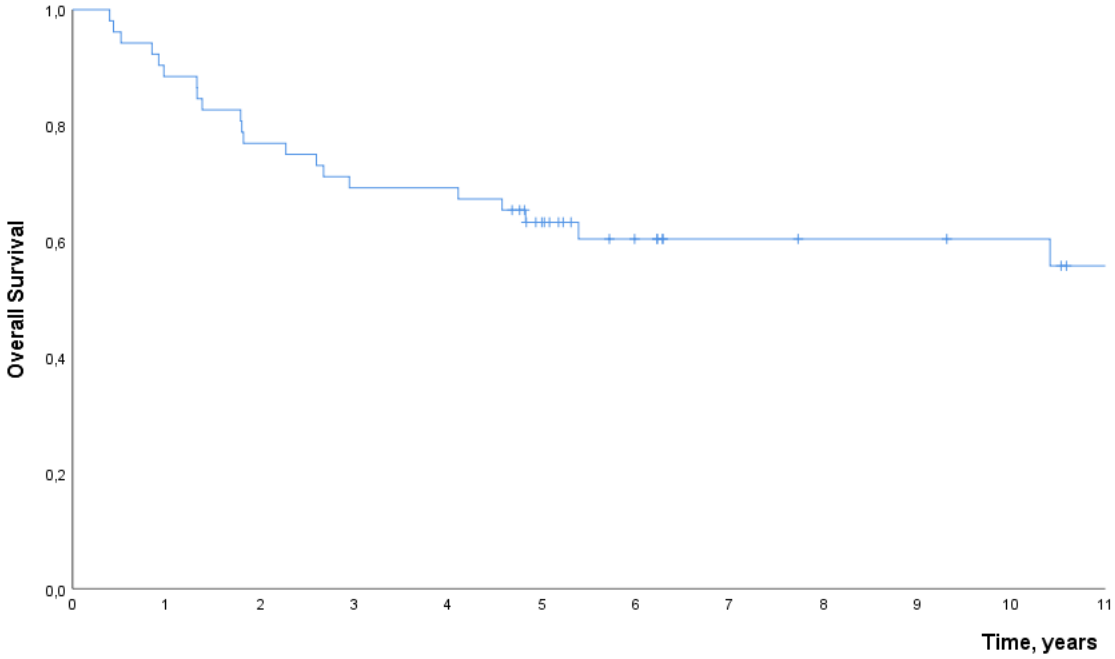

Figure 3. Overall survival by time for patients with radiation-associated sarcoma receiving curative treatment.